Table 1: Alpha-1 antitrypsin MM vs MZ subjects with COPD in COPDGene

Characteristic	MM	MZ	p
n	3962	162	
Age (years)	62.83 (8.67)	65.90 (8.00)	<0.001
Female (%)	1733 (43.7)	73 (45.1)	0.554
Non-Hispanic White (%)	2983 (75.3)	150 (92.6)	<0.001
Current smoker (%)	1789 (45.2)	35 (21.6)	<0.001
Smoking pack years	51.42 (27.21)	51.49 (27.49)	0.960
FEV$_1$ % predicted	57.74 (22.73)	52.85 (22.66)	0.004
FEV1/FVC	0.53 (0.13)	0.49 (0.14)	<0.001
BODE index	3.02 (2.59)	3.38 (2.75)	0.066
6-minute walk distance (ft)	1233.81 (407.51)	1207.16 (412.67)	0.352
SGRQ total score	36.59 (22.96)	38.87 (23.18)	0.135
MMRC dyspnea score	1.88 (1.47)	2.14 (1.47)	0.015
GOLD stage (%)			0.017
1	704 (17.8)	26 (16.0)	
2	1725 (43.5)	59 (36.4)	
3	1016 (25.6)	44 (27.2)	
4	517 (13.0)	33 (20.4)	
Percent emphysema	11.57 (12.15)	15.78 (14.21)	<0.001
Perc15	-933.77 (28.37)	-942.63 (28.03)	<0.001
Pi10	2.64 (0.60)	2.58 (0.51)	0.246
Segmental airway wall thickness	1.13 (0.24)	1.12 (0.23)	0.914

Data presented as mean (SD) or no. (%) MM: PI MM genotype; MZ: PI MZ genotype; COPD: chronic obstructive pulmonary disease; FEV$_1$: forced expiratory volume over one second; FVC: forced vital capacity; SGRQ: St. George's Respiratory Questionnaire; MMRC: Modified Medical Research Council; GOLD: Global Initiative for Chronic Obstructive Lung Disease; Percent emphysema: percentage of lung voxels with CT

attenuation $\leq$ -950 HU on inspiratory CT; Perc15: CT attenuation at the 15th percentile of the lung CT histogram; Pi10: Square root of the wall area of a theoretical airway with internal perimeter 10mm.

Table 2: Alpha-1 antitrypsin MM vs MZ subjects with COPD in LTRC

Characteristic	MM	MZ	p
n	544	25	
Age (years)	65.11 (9.49)	60.56 (7.41)	0.0180
Non-Hispanic White (%)	494 (90.8)	24 (96.0)	0.5960
Male sex (%)	298 (54.8)	12 (48.0)	0.6450
Current smoker (%)	41 (8.1)	1 (4.2)	0.7540
Smoking pack years	47.25 (33.18)	36.70 (23.23)	0.1240
Pre-bronchodilator FEV_1 % predicted	53.52 (25.20)	38.09 (22.98)	0.0030
Pre-bronchodilator FEV_1/FVC	0.51 (0.15)	0.40 (0.17)	0.0010
6-minute walk distance (ft)	1107.40 (346.23)	992.28 (382.86)	0.1490
SGRQ total score	36.12 (24.22)	51.29 (24.32)	0.0030
GOLD Stage (%)			0.0040
1	114 (21.0)	1 (4.0)	
2	219 (40.3)	9 (36.0)	
3	89 (16.4)	2 (8.0)	
4	122 (22.4)	13 (52.0)	
Percent emphysema	18.51 (14.40)	32.11 (16.29)	0.0010
Perc15	-946.59 (37.24)	-974.21 (24.00)	0.0060
Average of right and left mainstem wall area percentage (%)	43.89 (5.15)	43.23 (4.46)	0.6790
Average of right and left mainstem wall thickness	2.16 (0.33)	2.09 (0.30)	0.4990

Data presented as mean (SD) or no. (%) MM: PI MM genotype; MZ: PI MZ genotype; COPD: chronic obstructive pulmonary disease; LTRC: Lung Tissue Research Consortium; FEV_1: forced expiratory volume over one second; FVC: forced vital capacity; SGRQ: St. George's Respiratory Questionnaire; GOLD: Global Initiative for Chronic Obstructive Lung Disease; Percent emphysema: percentage of lung voxels with CT attenuation $\leq$ -950 HU on inspiratory CT; Perc15: CT attenuation at the 15th percentile of the lung CT histogram.

Table 3: Alpha-1 antitrypsin MM vs MZ subjects with COPD in ECLIPSE

Characteristic	MM	MZ	p
n	1684	100	
Age (years)	63.31 (7.15)	63.19 (6.40)	0.870
Female sex (%)	587 (34.9)	32 (32.0)	0.635
Non-Hispanic White (%)	1647 (97.8)	96 (96.0)	0.409
Current smoker (%)	610 (36.2)	27 (27.0)	0.078
Smoking pack years	48.35 (27.00)	47.21 (25.85)	0.682
FEV_1 % predicted	48.52 (15.54)	43.55 (16.48)	0.002
FEV_1/FVC	0.45 (0.11)	0.41 (0.11)	<0.001
BODE index	3.13 (2.08)	3.81 (2.42)	0.002
6-minute walk distance (ft)	1219.71 (398.89)	1194.72 (404.09)	0.553
SGRQ total score	48.34 (18.37)	49.82 (18.80)	0.437
MMRC dyspnea score	1.67 (1.05)	1.89 (1.16)	0.043
GOLD stage (%)			0.001
2	750 (44.5)	34 (34.0)	
3	720 (42.8)	41 (41.0)	
4	214 (12.7)	25 (25.0)	
Percent emphysema	17.03 (11.98)	22.67 (13.06)	<0.001
Perc15	-949.93 (50.30)	-970.79 (45.73)	<0.001
Pi10	4.40 (0.19)	4.38 (0.20)	0.325
Segmental wall area percent	65.77 (4.09)	64.91 (3.78)	0.048

Data presented as mean (SD) or no. (%) MM: PI MM genotype; MZ: PI MZ genotype; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume over one second; FVC: forced vital capacity; SGRQ: St. George's Respiratory Questionnaire; MMRC: Modified Medical Research Council; GOLD: Global Initiative for Chronic Obstructive Lung Disease; Percent emphysema: percentage of lung voxels with CT attenuation $\leq$ -950 HU on inspiratory CT; Perc15: CT attenuation at the 15th percentile of
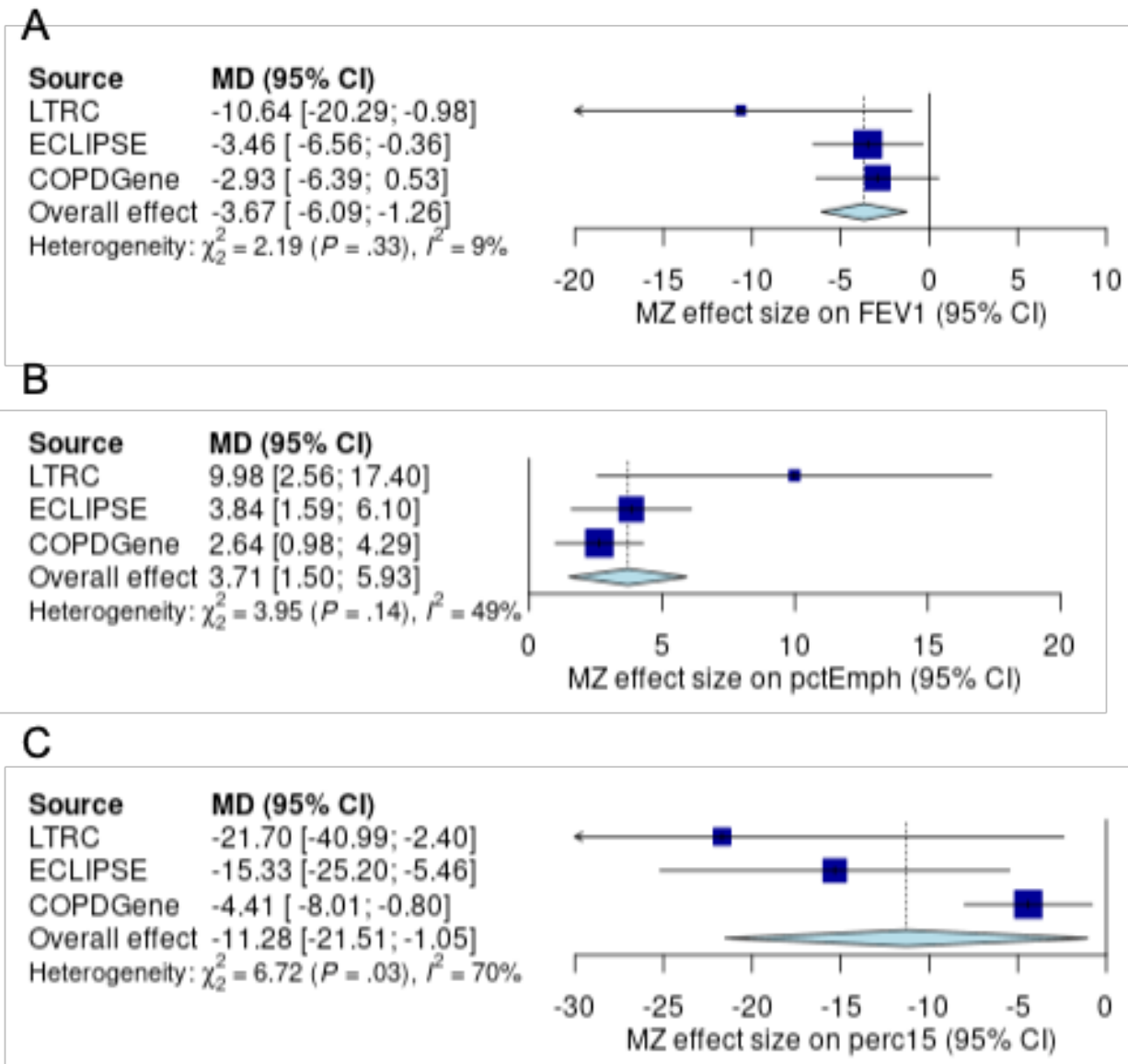
the lung CT histogram; Pi10: Square root of the wall area of a theoretical airway with internal perimeter 10mm.

Table 4: Multivariable analysis of effect of MZ on lung function and radiographic emphysema

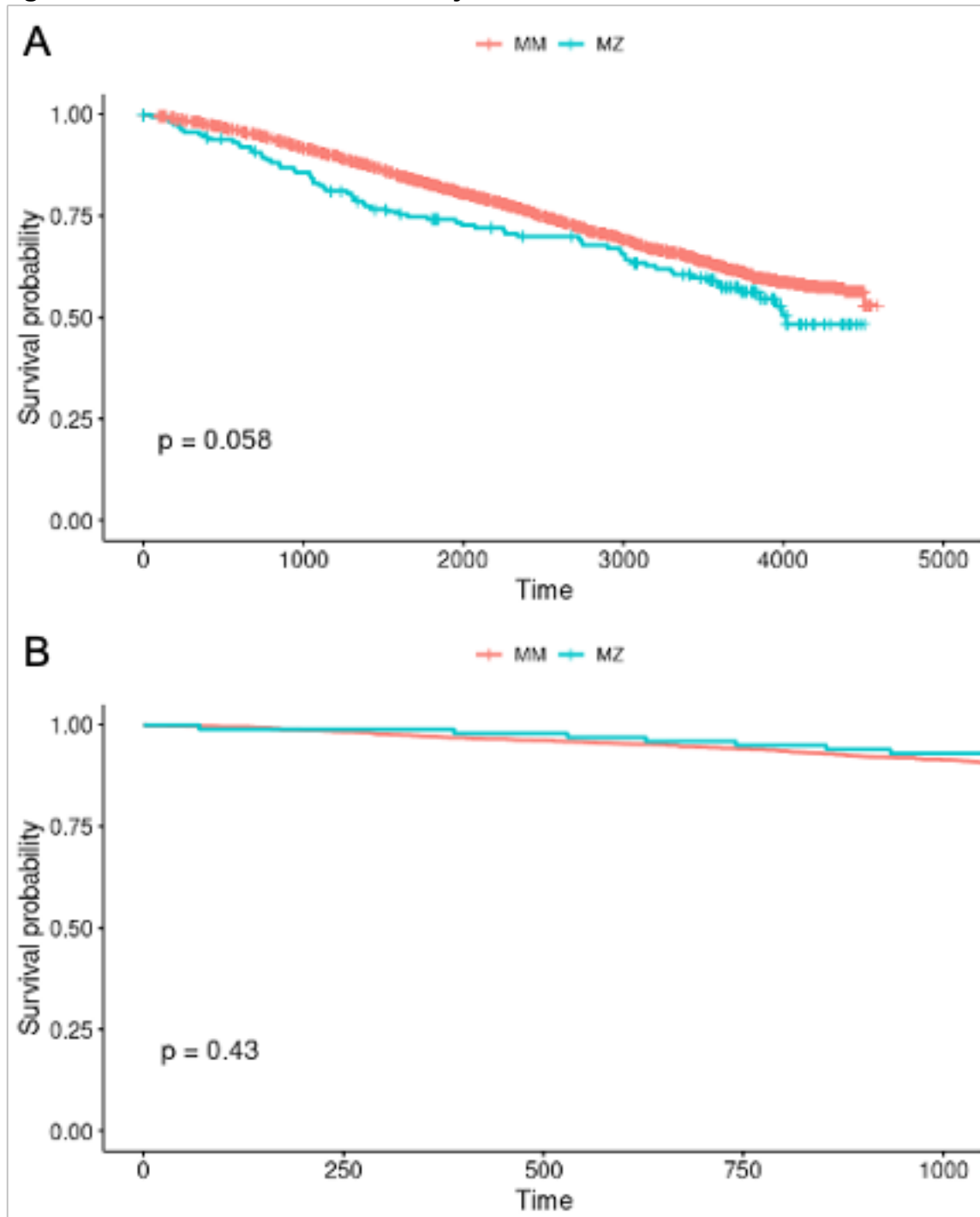| Measure	Study	Beta	SE	p
FEV$_1$ % predicted	LTRC	-10.64	4.93	0.0314
	ECLIPSE	-3.46	1.58	0.0287
	COPDGene	-2.93	1.77	0.0976
Percent emphysema	LTRC	9.98	3.79	0.0089
	ECLIPSE	3.84	1.15	0.0009
	COPDGene	2.64	0.84	0.0018
Perc 15	LTRC	-21.69	9.84	0.0283
	ECLIPSE	-15.33	5.03	0.0024
	COPDGene	-4.5405	1.84	0.0166

Data presented as linear regression effect estimates (Beta) and standard errors (SE). All regression models adjusted for age, race, gender, current smoking status, and smoking pack-years. Imaging outcome models additionally adjusted for body mass index and scanner model. MZ: PI MZ genotype; FEV$_1$: forced expiratory volume over one second; Percent emphysema: percentage of lung voxels with CT attenuation $\leq$ -950 HU on inspiratory CT; Perc15: CT attenuation at the 15th percentile of the lung CT histogram.

Figure 1: Meta-analysis of MZ effect sizes for lung function and CT emphysema
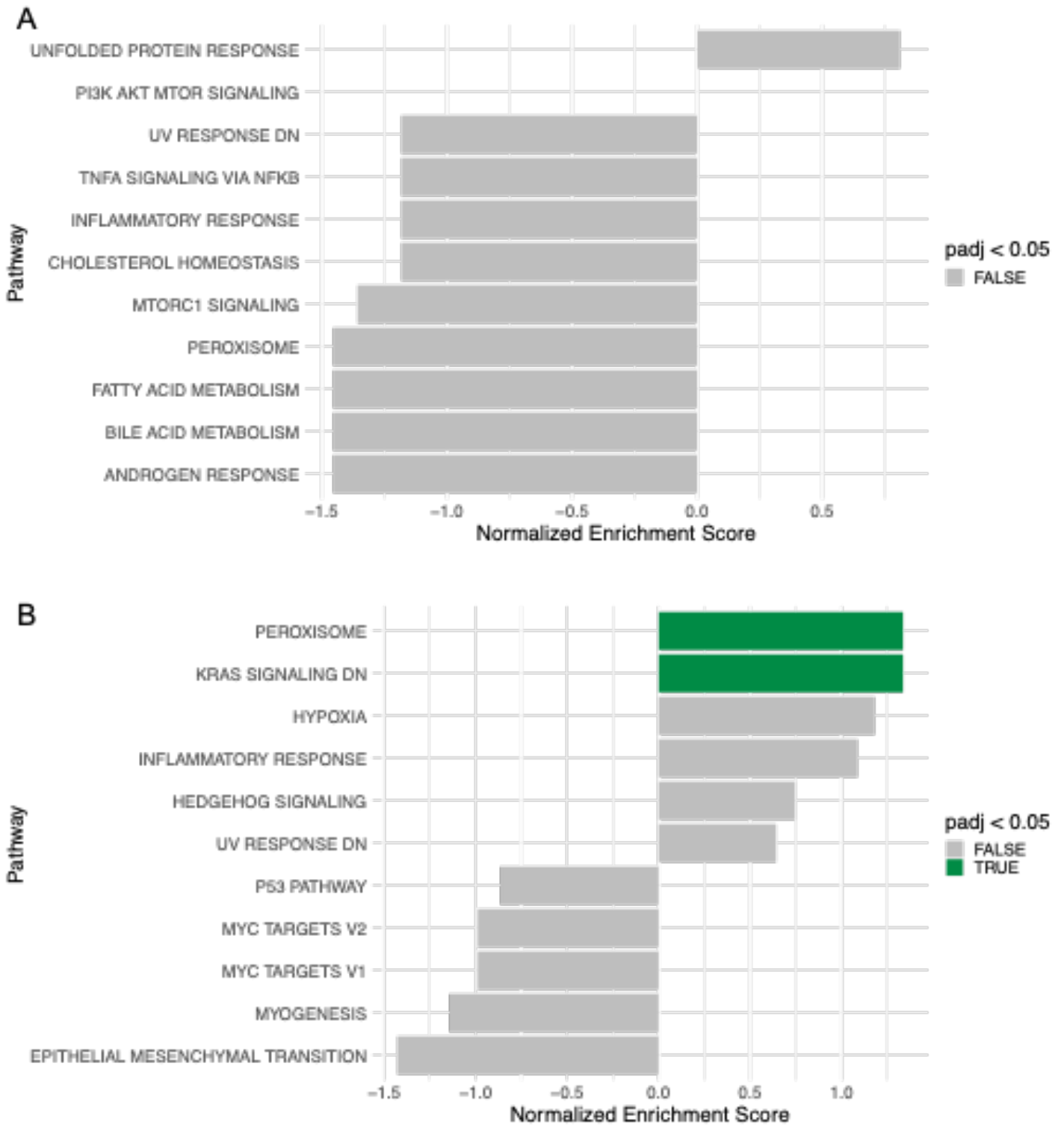

Meta-analyses of lung function and CT emphysema outcomes across LTRC, ECLIPSE, and COPDGene. Mean difference (MD) and 95% confidence interval (CI) shown. Heterogeneity estimated using DerSimoniam-Laird method. **A** Meta-analysis of effect sizes of MZ genotype on FEV$_1$ percent predicted. **B** Meta-analysis of effect sizes of MZ genotype on percent emphysema. **C** Meta-analysis of effect sizes of MZ genotype on perc15.

Figure 2: Survival in MM vs MZ subjects with COPD in COPDGene and ECLIPSE

Kaplan-Meier curves demonstrating survival probability in PI MM genotype subjects (orange line) compared to PI MZ genotype subjects (teal line). **A** Survival probability in COPDGene. **B** Survival probability in ECLIPSE.

Figure 3: Pathway analysis of nominally significant differentially expressed genes between MM vs MZ subjects with COPD

Enrichment of MSigDB hallmark pathways using nominally significant (p value < 0.001) differentially expressed genes. **A** Pathways enriched in differentially expressed genes using

RNA sequencing data from whole blood in COPDGene. **B** Pathways enriched in differentially expressed genes using RNA sequencing data from lung tissue in LTRC.